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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/515,582	02/29/2000	Roland Buelow	A-63708-5/RFT/JJD	9803

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/515,582	Applicant(s) BUELOW ET AL.
	Examiner Janice Li	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment and response filed on 6/26/02 has been entered and assigned as Paper # 12. Claims 26 and 27 are newly submitted. Claims 1-22, 26, and 27 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 1-13, and 16-22 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In paper #12, applicants argue that "modulators of HO-1" must be read in context of the entire claim, i.e. "nucleic acid that modulates heme oxygnease-I activity", and citing the definition in the specification as support for the argument, and conclude that applicants have clearly circumscribed the nature of nucleic acid modulators of heme oxygenase-I activity in cells.

The argument has been carefully considered but found not persuasive. This is because, the definition recites, "*For the most part, nucleic acid molecules that function to modulate HO-1 activity in cells will be nucleic acid molecules that encode a polypeptide that exhibits at least one biological activity that is normally associated with the human HO-1..., or with be antisense oligonucleotides whose sequences are derived from and/or based upon nucleotides 81-944 of the human HO-I...or non-coding sequences of a HO-I*". Apparently, the definition in the specification for a nucleic acid that modulates HO-1 is not limited to nucleic acids encoding HO-I and its variants, it encompasses numerous oligonucleotides that could serve as antisense to HO-I targeting both coding and non-coding regions of HO-I, any polypeptide that may influence HO-I activity in any way, e.g. transcriptional, translational, binding, degradation, any way of regulation, and these are only for "the most part" of the nucleic acids, the remain part of the nucleic acids have not been described. Claim 13 recites "a polypeptide having heme oxygenase-I activity", which virtually does not place any structural limitation on the polypeptide, which polypeptide may well be unrelated to HO-I, but possesses the function of HO-I somehow, which is yet to be discovered.

An adequate written description for a nucleic acid requires more than a mere statement that it is part of the invention. It is not sufficient to define the nucleic acid solely by its principal biological property, i.e. "**encoding a polypeptide that exhibits at least one biological activity that is normally associated with the human HO-1**", or "**antisense oligonucleotides whose sequences are derived from and/or based upon nucleotides 81-944 of the human HO-I...or non-coding sequences of a HO-I**",

because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any polynucleotide with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all nucleic acids that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. the structural characteristics or the sequences of a protein and nucleic acids, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of *all* or representative species of nucleic acids of the genus. Therefore, only the described HO-I and variants meet the written description provision of 35 U.S.C. §112, first paragraph.

Please note that this rejection has been modified in view of Exhibit J, *Schuller et al* (Nat. Structural Biol, 1999;6:860-67) submitted with Paper #12.

ENABLEMENT REQUIREMENT

The arguments drawn to using HO-I and variants at more than 80% sequence identity to HO-I are moot in view of new grounds of rejections that appear below.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for extending the survival of an organ transplant in a recipient comprising *ex vivo* perfusion of the organ transplant with a replication defective adenoviral vector encoding HO-I (Ad-HO-I) and variants prior to transplantation, wherein the organ is syngeneic, isogeneic, and allogeniec, wherein the variants have at least about 80% sequence identity to nucleotide 81-944 of SEQ ID. No: 1, does not reasonably provide enablement for extending the survival of any organ transplantation by *in vivo* cell contacting of Adv-HO-I, or using any nucleic acid that modulates heme oxygease-I activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Given the broadest reasonable interpretation, the claims embrace using any nucleic acid that modulates HO-I activity. As discussed in the preceding section, the specification fails to describe the sequences and common attributes of the genus of nucleic acids that modulate HO-I activity, the skilled artisan could not envision from the teachings of HO-I and variants, what would be other members of the genus, thus, would

not know how to use the invention without first carrying out undue experimentation to determine which of the nucleic acids would have the recited function.

As for antisense oligonucleotide, applicant are reminded that numerous factors complicating antisense gene therapy, which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. Even though the target molecule is known, picking and choosing the target region for the antisense oligo has proven to be unpredictable. *Patzel et al* (Nature Biotech 1998 Jan;16:64-68) states "THE SUCCESS OF ANTISENSE THERAPEUTICS IS NOT PREDICTABLE DESPITE THEIR WIDESPEREAD USE IN BIOTECHNOLOGY AND MOLECULAR MEDICINE. THE RELATIONSHIP BETWEEN RNA STRUCTURE AND BIOLOGICAL EFFECTIVENESS IS LARGELY NOT UNDERSTOOD...". (abstract) *Roush* (Science 1997 May;276:1192-3) teaches: "FOR SOME REASON, ANTISENSE OLIGOS BIND TO SOME SEQUENCES WITH MUCH GREATER AFFINITY THAN OTHERS" and "RANDOMLY MAKING ANTISENSE OLIGOS GIVES RANDOM RESULTS, AND WHEN IT WORKS, IT'S LUCK" and repots that companies have "FOUND SUCCESS BY SIFTING THROUGH DOZENS OF OLIGOS THAT COMPLEMENT SLIGHTLY DIFFERING SEGMENTS OF THE TARGETED MRNA, AND SELECTING THOSE THAT WORK." (page 1193, column 1). Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy and antisense technology, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regiments. However, the specification fails to provide even one such oligonucleotide that would actually modulate HO-I activity.

Further, the teaching of the specification calls for overexpression of HO-I, it is unclear the mechanism that the antisense to HO-I, which most likely would downregulate HO-I, could extend the survival of an organ graft, particularly an allogenic or xenogenic organ graft.

Given the broadest reasonable interpretation, the claims embrace using any viral vectors for expression of HO-I, however, the only teaching in working examples and subsequently submitted post-filing art use only adenoviral vector for gene expression. In view of the viral delivery systems in the pertinent art at the time of the effective filing date, several different vector systems are available for somatic gene transfer. These include DNA (either naked or complexed), RNA virues (retroviruses), and DNA viruses (adenovirus, adenoassociated virus, herpesvirus and poxvirus). Each of the systems has perceived advantages and disadvantages, which influence their selection for current or projected clinical applications. Whether the recited vectors are suitable for the purpose of the instant invention are unclear. For example, adenoviral vector is efficient in cell entry and wide range of host cells, but highly immunogenic and remain episomal, difficult to obtain long-term stability, thus better suited for use in vaccination or transient gene expression; transfection of retroviral vector is limited to dividing cells; AAV requires replicating adenovirus (helper virus) to grow and has very limited insert size. Herpes are highly immunogenic and the transgene is shut down within one week after infection for a variety of target cells, (*Robbins et al*, Pharmacol Ther 1998;80:35-47, sections 2.2, 2.3 particularly) therefore, they would not be suitable for long term delivery of HO-I. Herpes and poxviruses are also highly immunogenic. Naked DNA is extremely

inefficient in entry, and no mechanism for persistence or stability. (*Orkin et al*, Dec. 1995, pages 21-23, 30-32). The specification provides a brief overview of candidate vectors and elements in the recombinant vectors. However, the specification does not provide an enabling disclosure as to whether such vectors would achieve the recited effects *in vivo* concerning aspects of art-known difficulties. *Miller et al* (1995, FASEB J., Vol. 9, pages 190-199), acknowledge various vector system available in the art, then teach, "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR GENE TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES" (1st paragraph, page 198). The specification fails to teach how to overcome the art known difficulties to achieve efficient systemic delivery, therefore, fails to provide sufficient guidance for the skilled artisan to practice the invention without first carrying out undue experimentation.

Given the broadest reasonable interpretation, the claims further embrace contacting graft cells *in vivo* (administering a nucleic acid to the graft recipient). While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, *Miller et al.* teaches "FOR THE LONG-TERM SUCCESS AS WELL AS THE WIDESPREAD APPLICABILITY OF HUMAN GENE THERAPY, THERE WILL HAVE TO BE ADVANCES...TARGETING STRATEGIES OUTLINED IN THIS REVIEW, WHICH ARE

CURRENTLY ONLY AT THE EXPERIMENTAL LEVEL, WILL HAVE TO BE TRANSLATED INTO COMPONENTS OF SAFE AND HIGHLY EFFICIENT DELIVERY SYSTEMS" (page 198, column 1). *Deonarain* is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Verma et al.* (1997) reviews various vectors known in the art for use in gene therapy and the problems associated. *Verma* discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242). *Crystal* also reviews various vectors known in the art and indicates "AMONG THE DESIGN HURDLES FOR ALL VECTORS ARE THE NEED TO INCREASE THE EFFICIENCY OF GENE TRANSFER, TO INCREASE TARGET SPECIFICITY AND TO ENABLE THE TRANSFERRED GENE TO BE REGULATED" (page 409). While applicants' specification supports efficient transfer of HO-I by *ex vivo* organ perfusion, the specification fails to teach one of skilled in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer could be achieved by any delivery vectors. The specification fails to teach <u>any</u> specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Given the broadest reasonable interpretation, the claims further embrace allogeneic and xenogeneic transplantation, although applicants provide certain post-

filing art to support the claimed subject matter, they are not sufficient to support the full scope of the claimed invention. For example, *Soares* reference (IDS/33) suggests that cardiac xenograft survival is functionally associated with HO-1 gene up-regulation, however, they use the combination of a polypeptide (CVF) and cyclosporin A, not a nucleic acid, and organ grafts were pretreated for two days before the transplantation. *Blydt-Hansen* reference (Exhibit 15) teaches kidney perfusion with AD-HO1 24hr prior to orthotopical transplantation. Experiments of exhibits 16-18 are performed using Adv-HO1 perfusion 24 hr before the heart implantation. These references are insufficient as support for claims encompassing any nucleic acid that modulates HO-I activity, and by *in vivo* administration after or at the time of the transplantation.

Accordingly, in view of the quantity of experimentation necessary to determine the effect of extending the survival of an organ graft, particularly an allograft or xenograft, the lack of direction or guidance provided by the specification with regard to the breadth of the claims directed to the use of numerous therapeutic nucleic acids/vectors/in vivo administration, it would have required undue experimentation for one skilled in the art to practice the claimed invention as they are broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation "a nucleic acid that modulates heme oxygenase-I activity". The term "modulates" embraces up-regulation and down regulation, it is unclear what kind modulation the claim embraces, thus, the metes and bounds of the claims are unclear.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 27, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER